Health Canada Santé Canada

SUMMARY BASIS OF DECISION (SBD)

LEVEMIR®

Insulin Detemir, 100 U/mL, solution for injection

Novo Nordisk Canada Inc.

Submission Control No. 081683

Date Issued	2006/08/09

Health Products and Food Branch

Canada

Our mission is to help the people of Canada
maintain and improve their health.
Health Canada

HPFB's Mandate is to take an integrated approach to managing the health-related risks and benefits of health products and food by:

- minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,
- promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.

Health Products and Food Branch

Également disponible en français sous le titre : Sommaire des motifs de décision (SMD), LEVEMIR^{MD}, Insuline detemir, 100 U/mL, solution pour injection, Novo Nordisk Canada Inc., N^{o} de contrôle de la présentation 081683.

FOREWORD

Health Canada's Summary Basis of Decision (SBD) documents outline the scientific and regulatory considerations that factor into Health Canada regulatory decisions related to drugs and medical devices. SBDs are written in technical language for stakeholders interested in product-specific Health Canada decisions, and are a direct reflection of observations detailed within reviewer reports. As such, SBDs are intended to complement and not duplicate information provided within the Product Monograph.

Readers are encouraged to consult the 'Reader's Guide to the Summary Basis of Decision - Drugs' to assist with interpretation of terms and acronyms referred to herein. In addition, a brief overview of the drug submission review process is provided in the Fact Sheet entitled 'How Drugs are Reviewed in Canada'. This Fact Sheet describes the factors considered by Health Canada during the review and authorization process of a drug submission. Readers should also consult the 'Summary Basis of Decision Initiative - Frequently Asked Questions' document. These documents are all available on the Health Canada website.

The SBD reflects the information available to Health Canada regulators at the time a decision has been rendered. Subsequent submissions reviewed for additional uses will not be captured under Phase I of the SBD implementation strategy. For up-to-date information on a particular product, readers should refer to the most recent Product Monograph for a product. For information related to post-market warnings or advisories as a result of adverse events, interested parties are advised to access the Health Canada website.

For further information on a particular product, readers may also access websites of other regulatory jurisdictions, available under 'Related Links' on the Health Canada website. The information received in support of a Canadian drug submission may not be identical to that received by other jurisdictions.

Other Drug Policies and Guidance:

Readers should consult the Health Canada website for other drug policies and guidance documents. In particular, readers may wish to refer to the 'Management of Drug Submissions Guidance'.

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1 PRODUCT AND SUBMISSION INFORMATION

Brand Name	Levemir®
Manufacturer/Sponsor	Novo Nordisk Canada Inc.
Medicinal Ingredient	Insulin Detemir
International Non-proprietary Name	Insulin Detemir
Strength	100 U/mL
Dosage form	Solution for Injection
Route of Administration	Subcutaneous Injection
DINs	02271842 – Levemir® Penfill® (cartridge) 02271850 – Levemir® FlexPen® (pre-filled pen) 02271869 – Levemir® InnoLet® (pre-filled doser)
Pharmaco-therapeutic group (ATC Code)	Anti-Diabetic Agent, Insulin Analogue
Non-medicinal Ingredients	Mannitol, sodium chloride, disodium phosphate dihydrate, zinc acetate, phenol, metacresol, sodium hydroxide, hydrochloric acid and water for injection
Submission Type and Control No.	New Drug Submission, Control No. 081683
Date of Submission	2002/12/13
Date of Authorization	2005/09/29

2 NOTICE OF DECISION

On September 29, 2005, Health Canada issued a Notice of Compliance to Novo Nordisk Canada Inc. for the drug product Levemir®.

Levemir® contains the medicinal ingredient insulin detemir which is an anti-diabetic agent.

Levemir® is indicated for the treatment of adult patients with type 1 or type 2 diabetes mellitus who require a long acting (basal) insulin for the maintenance of normal glucose control. The prolonged action of Levemir® is mediated by the slower systemic absorption of insulin detemir molecules from the injection site due to strong self-association of the drug molecule and by albumin binding via the fatty acid side-chain.

The market authorization was based on data from adequate quality (chemistry and manufacturing), preclinical, and clinical information submitted. The efficacy and safety of Levemir® were studied in open-label, randomized, active control, parallel studies involving several thousand patients. Levemir® achieved the desired level of glycemic control along with decreased variability in fasting glucose levels in both type 1 and type 2 diabetes mellitus. The data submitted demonstrate that Levemir® can be administered safely when used under the conditions stated in the Product Monograph.

Levemir® (100 U/mL insulin detemir) is presented as a solution for injection in a cartridge, in a pre-filled pen, or in a pre-filled doser. The drug should be administered once or twice daily, based on the advice of the physician, in accordance with the needs of the patient. Dosing guidelines are available in the Product Monograph.

Levemir® is contraindicated during episodes of hypoglycaemia and in patients hypersensitive to Levemir® or one of its excipients. Detailed conditions for the use of Levemir® are described in the Product Monograph.

Based on the Health Canada review of data on quality, safety, and effectiveness, Health Canada considers that the benefit/risk profile of Levemir® is favourable for the treatment of adult patients with type 1 or type 2 diabetes mellitus who require a long acting (basal) insulin for the maintenance of normal glucose control.

3 SCIENTIFIC AND REGULATORY BASIS FOR DECISION

3.1 Quality Basis for Decision

3.1.1 Drug Substance (medicinal ingredient)

Description

Levemir® (insulin detemir) is a recombinant human insulin analogue. It differs from human insulin in that the amino acid molecule in position B30 has been omitted and a 14-C fatty acid chain has been attached to position B29. These changes produce a soluble insulin with a strong self-association ability, a slower systemic absorption from the injection site, and a stronger tendency to bind to albumin in the interstitial fluid of the subcutaneous tissue and plasma. The result is a protracted and more even release of insulin, producing a flatter blood glucose (BG) time curve and better glycemic control.

Manufacturing Process and Process Controls

Insulin detemir drug substance is produced by recombinant DNA technology in yeast cells. Master and working cell banks containing the genetically modified human insulin precursor material have been thoroughly characterized and tested for identity, genetic stability, and absence of adventitious contaminants.

Although the up-stream manufacturing processes of fermentation and recovery steps for insulin detemir are essentially identical to that for the conventional production of human insulin, the down-stream manufacturing processes of modification and purification steps are specific for insulin detemir. Following fermentation and recovery, the human insulin precursor is converted into insulin detemir by enzymatic cleavage, acylation, and a series of purification steps, which are unique to Levemir®.

All raw materials used in the manufacture of insulin detemir are considered to be suitable and meet standards appropriate for their intended use.

The manufacturing process consistency is adequately demonstrated through well defined and validated production procedures, in-process control limits, critical quality control tests, and the insulin detemir certificate of analysis specifications.

Characterisation

Several detailed characterisation studies including physico-chemical and biological testing were performed to demonstrate that the insulin detemir drug substance manufactured for both clinical studies and commercial production consistently exhibits the desired characteristic structure.

The product-related and process-related impurities were also identified and characterised.

Control of Drug Substance

Validation reports are considered satisfactory for all analytical procedures used for in-process and release testing of the drug substance and to justify the specifications of the drug substance.

Test results for 24 batches were provided. Data from the batch analyses were reviewed and considered to be acceptable according to the specifications of the drug substance.

The levels of product-related and process-related impurities were adequately monitored throughout the manufacturing process. Results from process validation reports and in-process controls indicated that the impurities of the drug substance were adequately under control. The level of impurities reported for the drug substance was found to be within the established limits.

A suitable and fully qualified container/closure system was utilized for the bulk drug substance storage and transfer.

Stability

Sufficient data based on accelerated and real-time stability studies have been provided to demonstrate that the insulin detemir drug substance is stable over the proposed shelf-life when packaged and stored under the specified conditions.

The analytical test methods used for the stability studies, at all time points, are identical to the analytical methods used for the insulin detemir drug substance specification release testing.

3.1.2 Drug Product

Description and Composition

Levemir® is a clear colourless solution for subcutaneous injection. It contains 100 U/mL of the medicinal ingredient insulin detemir. One unit (U) of Levemir® corresponds to one international unit (IU) of human insulin. The non-medicinal ingredients of insulin detemir are mannitol, sodium chloride, disodium phosphate dihydrate, zinc acetate, phenol, metacresol, sodium hydroxide, hydrochloric acid, and water for injection.

The primary container/enclosure system used for Levemir® is the Penfill® 3 mL cartridge, made of Type I glass, with a bromobutyl rubber plunger and a cap with laminated rubber.

Levemir® is supplied in the following presentations, with the identical composition and strength of 100 U/mL:

- Penfill® 3 mL cartridge
- InnoLet® (primary packaging: Penfill® 3 mL cartridge)
- FlexPen® (primary packaging: Penfill® 3 mL cartridge)

Levemir® Penfill® cartridges are designed for use with Novo Nordisk Insulin Delivery Systems and Novofine® needles. Levemir® InnoLet® (disposable doser) and FlexPen® (pre-filled disposable pen) are specifically designed for use with NovoFine® needles. All certifications required for qualification of the FlexPen® and InnoLet® design, materials, and devices are provided.

Pharmaceutical Development

The insulin detemir drug product is an aqueous sterile solution, at neutral pH, intended for subcutaneous (SC) injection in multi-dose presentation. The formulation includes an isotonic agent, preservatives, and several agents to optimize the stability of the preparation, including:

- **Mannitol** – used as an isotonic agent to modify the tonicity of the product
- **Sodium chloride** – added as a stabilizing agent to improve chemical stability
- **Disodium phosphate, dihydrate** – buffering agent to maintain pH for storage and use

- **Zinc acetate** – stabilizing agent with a positive effect on the physical stability of insulin detemir
- **Sodium hydroxide and hydrochloric acid** – pH adjustment if necessary
- **Phenol and metacresol** – added as preservatives

Except for metacresol, all excipients (formulation ingredients) used in the finished product were analysed according to and fulfilled the specifications in Ph. Eur.. Metacresol was analysed according to and fulfilled the specifications in USP.

Several studies which justified the type and proposed concentration of preservative/excipient to be used in the drug product were reviewed. These studies verified that there were no potential toxicological or immunological effects expected. The adequacy of the preservative system was determined to be compliant with the Ph. Eur..

Manufacturing Process and Process Controls

Levemir® drug product is formulated, sterile filtered and filled using proper aseptic processing techniques.

All manufacturing equipment and facilities, in-process manufacturing steps, and detailed operating parameters are adequately described, qualified, controlled and validated for performance within justified limits.

Control of Drug Product

Standard pharmacopoeial tests for appearance, identity, purity, content uniformity and sterility were performed for the Levemir® drug product in each of the three presentation formats.

Validation reports are considered satisfactory for all analytical procedures used for in-process and release testing of the drug product as well as to justify the specification of the drug product.

Data from final batch analyses were reviewed and considered to be acceptable according to the specifications of the drug product. Consistent batch production was adequately demonstrated for release and shelf-life specifications.

Through Health Canada's lot release testing and evaluation program, consistency lot samples from three consecutive lots of Levemir® drug product (in Penfill® 3 mL cartridge) were tested by the Biologics and Genetic Therapies Directorate, Health Products and Food Branch. The test results were evaluated and were found to meet the specifications of the Levemir® drug product.

The assembly processes for the FlexPen® and InnoLet® devices were fully validated. The critical features of the devices were identified and the device specifications were justified.

Stability

Sufficient stability study results based on long-term, accelerated, and severe condition testing have been provided and demonstrate that the Levemir® drug product is stable when packaged and stored under the specified conditions. The proposed 24 month shelf-life at 2-8°C, protected from light, is considered to be acceptable. In addition, an in-use period of 42 days at temperatures not exceeding 30°C is acceptable.

The analytical test methods used for these stability studies, at all time points, were identical to the analytical methods used for the Levemir® drug product specification and release testing.

3.1.3 Facilities and Equipment

Detailed information and data submitted for the equipment and facility involved in the manufacture of Levemir® were evaluated. The design, operations, and controls of the facility and equipment were considered suitable for the production of Levemir®.

3.1.4 Adventitious Agents Safety Evaluation

An evaluation of the risk of contamination with TSE as well as general microbiological and viral contamination was performed.

BSE/TSE Risk Evaluation

The bovine- and/or porcine-sourced primary raw materials used in the cell bank storage medium, and the bovine-sourced secondary raw material used in one of the purification steps, were evaluated for the risk of BSE/TSE transmission.

Based on the assessment of the geographic origin of the animals, the nature and sources of animal tissues/parts, and the manufacturing processes used for these raw materials, it was determined that the bovine- and porcine-sourced primary raw materials were of extremely low BSE/TSE risk. In addition, the bovine-sourced secondary raw material (bovine milk) was unlikely to present any risk of BSE contamination (per Office International des Epizooties (OIE) International Animal Health Code/Guidelines, CPMP Guideline "*Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*" (EMEA/410/01, Rev. 2), and Canadian Food Inspection Agency Policy).

Microbiological Risk Evaluation

All critical steps from raw materials to finished product were appropriately tested and controlled concerning bacteria and fungi.

Virus Risk Evaluation

The manufacturing process of insulin detemir in yeast cells did not impose any risk for the transmission of mammalian virus.

In conclusion, all raw materials used in the production of insulin detemir were considered safe with regard to the potential risks of BSE/TSE transmission or contamination with bacteria, fungi or viruses.

3.1.5 Summary and Conclusion

The New Drug Submission for Levemir® has undergone Quality (Chemistry and Manufacturing) review and was found to comply with the requirements of Section C.08.002 of the *Food and Drug Regulations* insofar as the Quality (Chemistry and Manufacturing) information is concerned.

The information provided for Levemir® demonstrates that the drug substance and drug product can be consistently manufactured to meet the approved specifications. Proper development and validation studies were conducted and adequate controls are in place for commercial production.

The manufacturer has been requested to keep their commitment of providing updated data/validation in support of column lifetimes as well as a 24 month stability report for drug product shortage when all data are available.

3.2 Non-clinical Basis for Decision

3.2.1 Pharmacodynamics

The pre-clinical pharmacodynamics (PD) of insulin detemir were examined mostly *in vitro*. A total of 6 non-clinical studies were reviewed. Of the 6 studies (5 *in vitro*, 1 *in vivo*), several factors were investigated including, the ability of insulin detemir to bind to albumin or to the human insulin receptor as well as its ability to stimulate tyrosine kinase and incorporate glucose into lipids.

The following were noted:

- Higher and tighter binding to albumin was observed for insulin detemir as compared to human insulin.
- Insulin detemir was less potent than human insulin in binding and activating the insulin receptor and in stimulating cellular glucose uptake. This reduction was in the order of 4-5 fold as compared to human insulin (varying between 4- and 10-fold in various assays).
- The formulation of Levemir® (2400 nmol/mL insulin detemir) was found to be equivalent to neutral protamine Hagedorn (NPH) insulin (600 nmol/mL) on an effect and volume basis. Thus, 1 unit (U) of Levemir® (24 nmol) corresponds to 1 U of human insulin (6 nmol).
- PD effects (measured by stimulation of tyrosine kinase and incorporation of radiolabelled glucose into lipids) were remarkably less potent (from 10-fold up to 50-fold) for insulin detemir than for human insulin.

3.2.2 Pharmacokinetics

Twenty-six pharmacokinetic (PK) studies (10 for absorption, 7 for distribution, 9 for metabolism, and 0 for elimination) were conducted on several animal models. Throughout the pre-clinical PK studies a 600 nmol/mL dosage of insulin detemir was used. This formulation was different from the one proposed for marketing. Bioequivalence studies between formulations (600 nmol/mL vs. 2400 nmol/mL) were not submitted.

Absorption

Absorption of radiolabelled (^{125}I- or ^{14}C-) insulin detemir was investigated in rats, mice and dogs following a single SC or intravenous (IV) dose. The substance was well absorbed with a bioavailability range of 38-60% in all species investigated which is comparable to results using soluble human insulin formulations. The approximate half-life ($t_{1/2}$) following SC administration was 1 hour in rats and 2 hours in dogs. In dogs, females exhibited a longer half-life (6.9 hours vs. 3.2 hours). The dog model exhibited non-linear PK behaviour. In the pre-clinical species tested, the elimination of insulin detemir from plasma following SC administration was only slightly slower than that following IV administration. This behaviour was due to the composition of the subcutis in rats and dogs being more serous (and less lipaemic), thinner and less tight in structure than in (most) humans.

Distribution

Tissue distribution of insulin detemir was studied in rats following single dose administration of ^{125}I-insulin detemir as well as single- and multiple- dose administration of ^{14}C-insulin detemir. The volume of distribution (V_z) was small, with typical values ranging from 0.1 to 0.2 L/kg, which is in accordance with a high level of plasma protein binding (>97%), mainly to serum albumin. Prolonged circulation in rats and dogs resulted from the high albumin binding in the plasma and interstitial fluid and was also mirrored by the V_z being relatively larger in mice than in rats and dogs. This was consistent with less protein binding in mice causing the compound to be more widely distributed than in rats and dogs.

Metabolism & Excretion

In the rat model, insulin detemir was metabolized to fatty acids and peptides. When incubated in liver cytosol from human, rat, dog, and pig models, or in kidney S9 mix from humans and rats, insulin detemir was broken down to an A and B chain. No substantial effect on cytochrome P450 was observed in the rat when insulin detemir was administered SC at a dose <50 U/kg/day. Following single or multiple dose of ^{14}C-insulin detemir, 24-53% of the dose was excreted in expired air, presumably as CO_2. Furthermore, 18-37% of the dose was found in the carcass 7 days after the last dose was administered indicating incorporation of the fatty acids or metabolites of the fatty acids into tissue components. In rats and dogs, metabolites excreted in their urine accounted for 13-26% of the dose.

3.2.3 Toxicology

The toxicity data base for insulin detemir is complete and is in accordance with the ICH Guidance S6: *Pre-clinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals Document*. Based on the results of sub-chronic rat and dog studies, it was determined that other than a decrease in blood glucose levels, there were few changes noted that were attributed to insulin detemir. Furthermore, there were no toxicological findings of concern.

Single-dose and Repeat-dose Toxicity

General toxicity was assessed after single-dose IV and SC administration to mice and rats and after repeat-dose SC administration to rats and dogs for up to 6 and 12 months respectively. These studies demonstrated no toxicity potential for insulin detemir other than effects directly or indirectly related to hypoglycaemia.

Mutagenicity

A standard set of experiments has been conducted involving the Ames test, the mouse micronucleus test, and test for chromosome aberrations in human lymphocytes. All tests were negative. It was concluded that insulin detemir was not mutagenic under the test conditions.

Mitogenicity

Native human insulin has, in addition to its metabolic actions, a weak mitogenic effect. Structural modifications to the insulin molecule could increase mitogenic potency, possibly resulting in growth stimulation of pre-existing neoplasms. Insulin detemir was compared to human and other insulins in a comprehensive study package in accordance with the Committee for Proprietary Medicine Products (CPMP) guidance document. Results from mitogenicity studies demonstrated that insulin detemir was less mitogenic than NPH insulin.

Carcinogenicity

In a 6-month rat study, there was no evidence of treatment-related oncogenicity (pre-neoplastic or neoplastic changes). It was concluded that there was no cause for concern regarding the carcinogenic potential of insulin detemir, therefore, no further *in vivo* carcinogenicity testing was considered necessary. The analysis of mitogenic potential, receptor binding, genotoxicity, and chronic rat studies conducted, demonstrates that insulin detemir has a similar or reduced carcinogenic potential as compared to NPH insulin.

Immunogenicity

Immunogenicity testing in rabbits indicated that the immunogenic potential of insulin detemir was lower than bovine insulin and similar to or lower than porcine insulin. In rat and dog studies antibody development was either absent or low, indicating that antibody inhibition of insulin detemir was not an issue in the toxicity studies.

Reproductive Toxicity

Results from embryofoetal development and reproduction toxicity studies revealed that insulin detemir and human insulin exhibit similar developmental/reproductive effects. Precautions for its use during pregnancy should therefore be similar to those listed for human insulin.

Safety Pharmacology

A total of 14 studies were submitted. After single-dose SC administration at a dose of up to 3 U/kg, insulin detemir was investigated and found to lack acute effect on the following physiological functions: cardiovascular and respiratory functions in the rat and dog, neuropharmacological function in mice, acetic acid induced writhing in mice, hexobarbiturate or alcohol induced sleep time in mice, pro- or anti-convulsant activity in mice, anti-pyretics in rats, and gastrointestinal motility. At a high dose, i.e. 30 U/kg, the following effects were observed: inhibition of spontaneous motor activity and an increase in both mean and diastolic blood pressure in rat, but decrease in diastolic blood pressure in dog. Results from the safety pharmacology studies indicated no safety concern when the dose was <30 U/kg.

In conclusion, the non-clinical toxicology testing in rats, dogs, and rabbits demonstrated that insulin detemir administered once daily as a SC injection was as safe as human insulin. Insulin detemir also exhibited a longer duration of action. Non-clinical safety testing of insulin detemir when administered twice daily by SC injection was not conducted.

3.2.4 Summary and Conclusion

Pre-clinical studies have demonstrated that insulin detemir is less potent than human insulin in binding and activating the insulin receptor and in stimulating cellular glucose uptake. To compensate for this difference, the concentration of the formulation was increased to four times the concentration of human insulin.

Levemir®'s protracted PD action is attributed to increased self-association and albumin-binding compared to human insulin. This delays absorption from subcutaneous sites into the bloodstream which in turn slows the distribution to target tissues.

A variety of toxicological tests have verified that insulin detemir is as safe as human insulin when administered once daily as a SC injection.

3.3 Clinical Basis for Decision

3.3.1 Human Pharmacology

The PK and PD properties of insulin detemir were investigated in healthy subjects, subjects with Type I or Type II diabetes mellitus, and in special populations including: Japanese subjects, elderly subjects, children and adolescents, and subjects with hepatic or renal impairment. The clinical pharmacology development programme consisted of 32 clinical trials: 24 in Europe, 3 in the U.S., and 3 in Japan. This is in addition to one other trial presented as short-term for safety analyses as well as a pilot study to set up a technique for the evaluation of the PK/PD of insulin detemir.

The following issues were addressed: population, effect of injection sites, potential drug accumulation after multiple doses, effect of hepatic or renal impairment on PK, inter-subject variability and bioequivalence of the formulations used for clinical evaluation. Insulin detemir is considered a long acting insulin product similar to NPH insulin.

3.3.2 Pharmacodynamics

The dose-response relationship and duration of action of the to-be-marketed (100 U/mL) insulin detemir preparation (injected SC) was investigated in subjects with Type I diabetes mellitus under isoglycemic clamp conditions. The mean glucose infusion rate (GIR) profiles for five SC insulin detemir doses ranging from 0.1 U/kg to 1.6 U/kg and one NPH insulin dose (0.3 IU/kg) were considered. Both the area under the glucose infusion rate (AUC_{GIR}) and the maximum GIR increased proportionally with increased doses of insulin detemir.

To determine the insulin detemir dose equipotent to 0.3 IU/kg of NPH insulin, the equivalent insulin detemir dose was interpolated from estimates of $AUC_{GIR(0-24h)}$. In terms of $AUC_{GIR(0-24h)}$, it was estimated that a dose of approximately 0.3 U/kg (0.29 U/kg) insulin detemir would give the same glucose lowering effect as 0.3 IU/kg NPH insulin with a GIR_{max} of 1.4 mg/kg/min.

The duration of action for insulin detemir was varied and apparently dose-dependent. It ranged from 6 hours at the lowest dose to approximately 24 hours at the highest for a range of doses including those that were clinically relevant.

3.3.3 Pharmacokinetics

A number of clinical pharmacology trials investigated PK after both IV and SC administration of insulin detemir in healthy and diabetic subjects.

Absorption, Distribution, and Metabolism

As was expected, due to the albumin binding properties of insulin detemir, clearance in the IV studies was lower (1.8 to 2.7 mL/min/kg across trials) than for human insulin (15.8 to 19.6 mL/min/kg across trials). Additionally, the initial half-life was longer (19 to 25 min – across trials) for insulin detemir versus 2.4 min for human insulin. The half-life after SC administration was considerably longer, being about 3 to 6 hours in healthy subjects and about 5 to 7 hours in subjects with Type I diabetes mellitus (in therapeutically relevant doses). The volume of distribution for insulin detemir was small (approximately 0.1 L/kg), which is expected for a highly protein bound drug and is in agreement with the albumin distribution space. The concentration gradient between serum and interstitial fluid was higher for insulin detemir.

Overall, the absorption PK profile of insulin detemir in subjects with Type I diabetes mellitus closely resembles that of healthy subjects. Insulin detemir was absorbed at a slightly slower rate in subjects with Type II diabetes mellitus than in those with Type I. Serum insulin detemir concentrations, as measured by $AUC_{(0-16h)}$ and C_{max}, tended to be lower for subjects with Type II diabetes mellitus. AUC and C_{max} were greater after administration of 0.75 U/kg than 0.38 U/kg for both groups. The smaller AUC observed for subjects with Type II diabetes mellitus may be related to the relatively short evaluation period (16 hours). The apparent difference in total exposure may have been less pronounced if the entire concentration-time profile had been assessed.

Absorption was evaluated in 28 healthy subjects after SC administration in the three most commonly used injection sites: the thigh, abdomen, and deltoid. The resulting data indicates that insulin detemir has slower absorption, smaller peak concentration, longer half-life, and slightly lower bioavailability following SC administration in the thigh as compared to the abdomen or deltoid.

$AUC_{(0-\infty)}$ and C_{max} increased proportionally with administered doses ranging from 0.1 to 1.6 U/kg. Steady state with insulin detemir was reached quite rapidly (by the end of 24 h after two doses administered at 12 hour intervals) and trough concentrations at this point were almost identical to those after 7 days of daily administration twice per day. No further accumulation was evident after the second dose on the first treatment day.

Special Populations

A cross-trial analysis demonstrated that there was no difference in PK between genders, however, one study did appear to show that absorption of insulin detemir was slower in males than in females following SC administration in the thigh. A trial investigating differences in PK in the elderly showed higher AUC for elderly subjects (69-85 years of age). This difference is not considered to be relevant to dosing recommendations. No consistent differences were found between the PK properties of insulin detemir in healthy Caucasian and Japanese subjects.

There did not appear to be any relevant effect of renal impairment on the PKs.

Hepatic impairment impacted the extent of bioavailability as estimated by $AUC_{(0-\infty)}$. There was a decrease in bioavailability with increasing degree of hepatic impairment (as shown in four groups: healthy, mild, moderate, and severe) where the $AUC_{(0-\infty)}$ for healthy subjects was 58% higher than that of subjects with severe hepatic impairment. The PK results were confounded, however, by unbalanced bodyweight between healthy subjects and subjects with moderate to severe liver impairment. A >40% smaller $AUC_{(0-\infty)}$ and 35-47% faster clearance were observed, however, in patients with severe/moderate liver insufficiency as compared to healthy subjects. The requirements for Levemir® may need to be adjusted in patients with hepatic impairment.

3.3.4 Clinical Efficacy

The efficacy of Levemir® was studied in multi-centre, randomized, parallel comparison, open label trials. Subjects had to have been diagnosed with Type I or Type II diabetes mellitus for $\geq$12 months and had to be $\geq$18 years old for Type I diabetics or $\geq$35 years for Type II diabetics. Subjects were required to have a BMI $\leq$35 kg/m^2, an Hb_{A1c} level

≤12.0%, an ability to measure glucose independently, and a basal insulin requirement of ≥30% of total daily dose. The starting dose for each subject was based upon each patient's previous insulin requirements. All doses were administered by SC injection.

Type I Diabetes Mellitus Trials

Three pivotal trials (6 months, 4 months, and 4 months) were conducted to compare the efficacy of insulin detemir to NPH insulin in a basal/bolus regimen, administered mainly twice daily. The total data base included 1038 insulin detemir patients and 517 NPH insulin patients.

The primary efficacy endpoint was the level of Hemoglobin$_{A1c}$ (Hb_{A1c}) at the end of the trials. The rationale for this measurement is based on the fact that glucose binds readily to subtype Hemoglobin A forming the glycosylated Hb_{A1c}. The decomposition of this process is relatively slow and overall Hb_{A1c} levels change gradually over approximately 10 weeks. The Hb_{A1c} level therefore represents the average BG level of roughly the last 8-12 weeks and can be used as an indicator of the average recent BG level.

The secondary efficacy endpoints included the fasting plasma glucose (FPG), 9 point BG profiles, variation in FPG, frequency of high and low BG excursions and fluctuations, bodyweight changes, and quality of life.

Table 1: Pivotal Type I Diabetes Mellitus Trial Summary

Pivotal Trial	Subjects per Group	Basal Insulin	Bolus Insulin	Trial Duration	Primary Endpoint
1	Insulin Detemir – 491 NPH Insulin – 256	Once Daily	Human Soluble Insulin	6 months	Hb_{A1c} after 6 months
2	Insulin Detemir – 139 (morning & dinner) Insulin Detemir – 132 (morning & bedtime) NPH Insulin – 129 (morning & bedtime)	Twice Daily	Insulin Aspart	4 months	Hb_{A1c} after 4 months

Pivotal Trial	Subjects per Group	Basal Insulin	Bolus Insulin	Trial Duration	Primary Endpoint
3	Insulin Detemir – 137 (12 hours apart) Insulin Detemir – 139 (morning & bedtime) NPH Insulin – 132 (morning & bedtime)	Twice Daily	Insulin Aspart	4 months	Hb_{A1c} after 4 months
4 (Safety Only)	Insulin Detemir – 161 Insulin Glargine – 159	Twice Daily	Insulin Aspart	26 weeks	Adverse Effects and Laboratory Tests

In all three pivotal studies, insulin detemir was non-inferior to NPH insulin with respect to the primary efficacy endpoint (Hb_{A1c} at end of trials). The FPG and variation in FPG were reduced in the insulin detemir groups in all three studies. The overall risk of hypoglycaemia was similar in the test and control groups but the frequency of nocturnal hypoglycaemia tended to be lower in the insulin detemir groups. Insulin detemir performed better with respect to nocturnal hypoglycaemia when it was given in the morning and at bedtime than when it was given at 12 hour intervals. Weight gain was less in all groups receiving insulin detemir but no explanation could be provided to clarify this phenomenon. It was noted however, that this was not due to poorer control of diabetes mellitus in these groups.

Type II Diabetes Mellitus Trials

Three pivotal trials were conducted (6 months, 6 months, and 22 weeks). Two were basal/bolus regimes comparing insulin detemir with NPH Insulin, once or twice daily. The other considered insulin detemir combined with an oral antihyperglycemic (Metformin or similar). The total data base included 845 insulin detemir patients and 521 NPH insulin patients. The primary efficacy endpoint and secondary efficacy endpoints were the same as for the Type 1 diabetes mellitus trials.

Table 2: Pivotal Type II Diabetes Mellitus Trial Summary

Pivotal Trial	Subjects per Group	Basal Insulin	Bolus Insulin	Trial Duration	Primary Endpoint
1	Insulin Detemir-341 NPH Insulin – 164	Once or Twice Daily	Insulin Aspart	6 months	Hb_{A1c} after 6 months
2	Insulin Detemir - 309 NPH Insulin – 158	Once Daily	Metformin and other oral antihyperglycemics	6 months	Hb_{A1c} after 6 months
3	Insulin Detemir - 195 NPH Insulin – 199	Once or Twice Daily	Insulin Aspart & Human Soluble Insulin	22 weeks	Hb_{A1c} after 22 weeks

Two of the three pivotal studies demonstrated non-inferiority of insulin detemir in comparison with NPH insulin. In the third study, insulin detemir was inferior to NPH insulin with respect to Hb_{A1c} levels at the end of the trial (primary efficacy endpoint). This latter trial was a combination of insulin detemir (or NPH Insulin) with an oral antihyperglycemic (Metformin or other). Based on these results, a statement was included in the Product Monograph that insulin detemir is intended for use in a basal/bolus regimen and that studies in combination with Metformin or other oral antihyperglycemic agents are ongoing. The secondary efficacy criteria were much the same in the test and control groups except for the subject variation in FBG which was reduced in the insulin detemir groups.

Non Pivotal Efficacy Trials

One trial was conducted. Due to the fact that it employed a 'not to be marketed' preparation it was only considered for safety and not for efficacy.

3.3.5 Clinical Safety

Type I Diabetes Mellitus Trials

Four pivotal studies (6 months, 4 months, 4 months, and 26 weeks – Table 1) were conducted. The total data base included 1199 insulin detemir patients, 517 NPH insulin patients, and 159 insulin glargine (glArg) patients. The safety criteria included the frequency of hypoglycaemia, presence of nocturnal hypoglycaemia or adverse events (AEs) and the formation of anti-insulin antibodies.

Treatment emergent AEs were equally distributed in frequency and severity between the test and control groups and no safety concerns specific to insulin detemir were identified

in any of the pivotal trials. In these studies, Levemir® and NPH insulin had a similar overall rate of hypoglycaemia. Nocturnal glucose profiles were flatter and smoother, and the risk of nocturnal hypoglycaemia was reduced (by 22%) for Levemir® as compared to NPH insulin. Mild local reactions at the injection site appeared to be more frequent with insulin detemir but were not considered a significant problem. Specific and non-specific antibody formation occurred in the insulin detemir groups but apparently did not impair insulin action. No studies were performed on subjects <18 years of age.

Four non-pivotal trials were conducted comparing insulin detemir with NPH insulin in a basal/bolus regimen. Each trial was 6 months in duration and two were extensions of the other two. The safety criteria were the same as those for the pivotal trials. The total data base included 907 insulin detemir patients and 603 NPH insulin patients. Treatment emergent adverse events were equally distributed between the test and control groups and no safety concerns specific to insulin detemir were identified.

Type II Diabetes Mellitus Trials

The three pivotal trials are described in Table 2. The safety criteria were the same as those of the Type I Diabetes mellitus trials.

Due to an apparently greater number of deaths in the insulin detemir groups the sponsor commissioned an independent meta-analysis to explore a possible relationship between cardiovascular and cerebrovascular events in the patients in the studies that used insulin detemir versus NPH Insulin. No relationship to trial medication was found. The clinical reviewer has perused the causes of death and has concluded that they can be attributed to existing medical conditions and could not be specifically attributed to insulin detemir. No other safety concerns were identified in the studies.

One non-pivotal trial was conducted. The duration of this study was 6 months and it included a total data base of 221 insulin detemir and 218 NPH insulin patients. No safety concerns specific to insulin detemir were identified.

Insulin detemir has been approved in the U.S. and in the European community. Safety studies did not identify any major concerns related to insulin detemir or significant differences between insulin detemir and NPH insulin.

Contraindications, Warnings, and Precautions

Levemir® is contraindicated during episodes of hypoglycaemia and in patients hypersensitive to Levemir® or one of its excipients. As with insulins in general, concomitant use of other drugs may influence insulin requirements.

3.4 Benefit/Risk Assessment and Recommendation

3.4.1 Benefit/Risk Assessment

The major benefit of Levemir® is that it is a basal insulin with a more predictable release pattern. Most clinical studies on patients with Type I diabetes mellitus demonstrated reduced within-patient variability of FBG. Several studies reported a reduced frequency of nocturnal hypoglycaemia while also achieving comparable diabetes mellitus control when compared to NPH insulin.

The safety of Levemir® is comparable to NPH insulin except that in several studies, nocturnal hypoglycaemia was generally less frequent with Levemir®. The higher death rate in patients using insulin detemir has been satisfactorily addressed by the sponsor. Nevertheless, post-marketing surveillance should monitor cardiovascular and cerebrovascular deaths in patients receiving insulin detemir. The benefits of Levemir® in cases of Type I diabetes mellitus outweigh the risks.

Levemir® was equally as effective as NPH insulin in Type II diabetes mellitus patients in controlling Hb_{A1c} levels and slightly better at reducing the variability of FBG. There were no significant safety concerns with the use of Levemir® in Type II diabetes mellitus patients. The benefits of insulin detemir in Type II diabetes mellitus patients also outweigh the risks.

3.4.2 Recommendation

Based on the Health Canada review of data on quality, safety and effectiveness, Health Canada considers that the benefit/risk profile of Levemir® (insulin detemir) is favourable for the treatment of adult patients (>18 years) with Type I or Type II diabetes mellitus who require a long acting (basal) insulin for the maintenance of normal glucose control. Its use is recommended in combination with short or rapid acting meal time insulin. The New Drug Submission complies with the requirements of sections C.08.002 and C.08.005.1 and therefore Health Canada has granted the Notice of Compliance pursuant to section C.08.004 of the *Food and Drug Regulations*.

4 SUBMISSION MILESTONES

Submission Milestone	Date
Submission filed	2002/12/13
Screening	
Screening Deficiency Notice issued	2003/01/27
Response filed	2003/03/10
Screening Acceptance Letter issued	2003/04/03
Review	
Clinical Evaluation complete	2005/09/16
Quality Evaluation complete	2005/07/28
Labelling Review complete	2005/09/23
NOC issued by Director General	2005/09/29